Remarks

Reconsideration of this Application is respectfully requested.

Claims 9-16, 21 and 23-26 are pending in the application. Claims 9-16 and 21 stand rejected.

The new claims are supported at least by the originally filed claims. Additional support for claim 23 can be found at page 18, lines 7-9 and additional support for claims 24-26 can be found at page 18, lines 8-12.

Applicants thank the Examiner for withdrawal of the previous rejections under 35 USC §§ 102 and 103.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection Under 35 USC §112, First Paragraph

The Examiner has rejected claims 9-16 under 35 USC §112, first paragraph as alleged not enabling any person skilled in the art to which it pertains, or with which it is most closely connected, to make the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

Specifically at page 3 the Examiner states:

> Therefore, in summary, the breadth of the claims is excessive regarding Applicants claiming any and all nucleic acid molecules comprising any and all alterations (additions, deletions, substitutions) of any part of its 3'-UTR other than the full replacement of this region in the rabbit beta-globin mRNA. Applicants have provided no guidance or working examples of any nucleic acid construct with an altered 3'-UTR other than that of a globin protein, nor have Applicants provided any guidance or working examples of any globin construct with any type of alteration in the 3'-UTR region other than a replacement of the entire 3'-UTR. It would also

> not be predictable to the artisan which portions of the 3'-UTR to alter, substitute, or delete, in order to redirect the protein to the ER. For these reasons, the Examiner holds that undue experimentation is required to practice the claimed invention.

Applicants respectfully disagree.

Applicants have already overcome this rejection as acknowledged in the Office Action of October 29, 2001 (Paper 11) and respectfully request clarification concerning why it is being made again. In the Office Action of April 23, 2001 (Paper 8) at page 3, first full paragraph, the Examiner stated that "the breadth of the claims is extensive with regard to claiming all nucleic acids constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region. . . Applicants do not provide enough guidance or working examples of nucleic acid constructs. . . It is not predictable to one of ordinary skill in the art what these critical nucleic acid residues . . . allow the targeting of these molecules to the desired location in the cell." Clearly, the Examiner's previous rejection is similar to that currently being raised.

In response to the rejection in the April 23, 2001, Applicants filed a reply on August 23, 2001 and provided the following beginning at page 4:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Some experimentation is permitted so long as the experimentation necessary to practice the invention is not undue. *In re Angstadt,* 537 F.2d 498, 504 (CCPA 1976).
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> The present invention establishes, *inter alia*, the principle that the addition of a nucleic acid encoding a signal peptide sequence to an mRNA encoding an intracellular protein is not sufficient to target that mRNA to the endoplasmic reticulum (ER). In fact, as established by Applicants' disclosure, it is also necessary to modify and/or

replace the native 3'UTR of the mRNA encoding the intracellular protein in order to remove any naturally-occurring signals which may affect or compete with the directing ability and efficiency of the signal peptide sequence. Accordingly, claim 9 is directed to a nucleic acid which allows a non-secreted protein to be synthesized in the ER (from where it can be secreted) and not in "an intracellular location other than the endoplasmic reticulum or . . . free and/or cytoskeletal bound polysomes." *See* claim 9. Thus, contrary to the Examiner's assertion that "Applicants desire nucleic acid molecules in which can be targeted to the ER, *FP, or CBPs*," (emphasis added) the claimed invention envisions *targeting* to only the ER.

In support of the rejection, the Examiner has asserted that "breadth of the claims is extensive with respect to all or part of a 3' untranslated region." Paper No. 8, page 3. The Examiner has further asserted that "Applicants do not provide enough guidance or working examples of nucleic acid constructs comprising a deletion, insertion, or substitution in respect to all or part of a 3' untranslated region" and "since the 3'-untranslated region is critical for targeting, it would be necessary to know the effect that a mutation in this region has on this targeting." *Id.* From the Examiner's objections, it is clear that the objection extends only to the portion of the 3'UTR to be deleted, inserted, or substituted. Applicants assert that the specification clearly enables one of ordinary skill in the art to delete, insert or substitute the whole of a 3'-UTR.

Specifically, the Examiner believes that "[i]t is not predictable to one of ordinary skill in the art what these critical nucleic acid residues in the 3'-untranslated region are which allow the targeting of these molecules to the desired locations in the cell." *Id.* Applicants respectfully disagree. As is clear from the specification, the invention is concerned with altering or removing the native 3'UTR of the non-secreted protein so that its effect in intracellular targeting is negated and the heterologous signal peptide can direct synthesis in the ER. *See* Specification, page 4, lines 8-19. Therefore, one of ordinary skill in the art, need not know which residues "allow the targeting of these molecules to the desired locations in the cell." One of ordinary skill in the art need only know whether the 3'UTR has been sufficiently disrupted to negate its intracellular targeting effect. As described on page 4, lines 15-19 and in the examples, this can be determined without undue experimentation using a reporter gene and hybridization assays. Routine

> experimentation does not vitiate enablement of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (1988).
>
> The disruption of the native 3'UTR such that its effect in intracellular targeting is negated can be considered to be similar to the disruption of cell-or temporal-specific promoter regions. If the promoter region is to be disrupted, one of ordinary skill in the art would simply carry out routine experiments in which the promoter region has insertions, substitutions or, most likely, deletions in order to obtain disruption. One of ordinary skill in the art would not be interested in which specific nucleic acid residues provide the specific activity of the promoter. Rather, one of ordinary skill in the art would be interested in providing a modified version of the promoter which does not have the native activity.

Following the Reply of August 23, 2001, the Examiner stated in the Office Action of October 29, 2001 that "All rejections under 35 USC 112, first paragraph have been withdrawn in view of Applicants' arguments that one of ordinary skill in the art ***would know whether the 3'UTR has been sufficiently disrupted to negate its intracellular targeting effects***." (Emphasis added). Applicants reiterate the above arguments made in the reply of August 23, 2001 in order to overcome the current §112 rejection and respectfully request the Examiner to explain the reversal of the previous withdrawal of the rejection and why such arguments are no longer convincing. If the Examiner continues to maintain the rejection, he is respectfully requested to specifically address each and every point of the argument presented above.

In the Office Action at page 3, first paragraph, the Examiner also referred to Figure 3 stating that "Figure 3 of the instant specification is unclear and appears that all that is required for increased localization of mRNA to the ER is a signal sequence (see construct 'SSGG') and not any alteration of the of the 3'-UTR. Clarification of this issue is respectfully requested."

Referring to Figure 3, a number of different mRNAs were analyzed for the polysomes to which they were directed. mRNA encoding cytoplasmic proteins is directed to free polysomes, that encoding cytoskeletal or nuclear proteins is directed to cytoskeletal bound polysomes, and that encoding secreted proteins is directed to membrane-bound polysomes.

Signal sequence (SS) nucleotides from rat albumin were introduced into the globin mRNA (construct SSGG), resulting in redirection of the mRNA to membrane-bound polysomes. Retargeting of globin mRNA was successful.

Next, native globin 3' UTR of construct SSGG was replaced with the 3' UTR from c-myc (an intracellular protein), resulting in the construct SSGM. As can be seen from Figure 3, there is a clear effect of the c-myc 3' UTR on retargeting. In this example (construct SSGM), retargeting of globin mRNA was not successful. Referring to Figure 6B, however, the replacement of the c-myc 3' 3' UTR with the albumin 3' UTR (construct SSGA) resulted in the mRNA being redirected to membrane bound polysomes in the same manner as SSGG. The results discussed above demonstrate the importance of the 3' UTR in targeting mRNA to membrane-bound polysomes and that the 3' UTR can override the effects of a signal sequence in redirecting an mRNA to membrane-bound polysomes. Therefore, it is important to disrupt the 3' UTR so that any effect that this has in directing the mRNA to locations other than the membrane-bound polysomes is eliminated or reduced.

The Examiner also stated at page 3 that "both wild-type globin and c-myc appear to be targeted, at least in part, to the ER (Figure 3). . ." As explained above, Figure 3 shows ***only*** the distribution of globin mRNA and does not relate to c-myc. Therefore, this aspect of the rejection is overcome.

The Examiner further suggests that Figure 3 shows that wild type globin mRNA (GG) is partially targeted to the membrane-bound polysomes (ER). While small amounts of mRNA may appear in membrane-bound polysomes in Figure 3 for construct GG, these should not be regarded as targeted mRNA. First, in the transfected cells, there is considerable overexpression of the transfected gene. Thus, the cell can become "flooded" with the mRNA for the transfected gene and can as a result become bound to all types of polysomes. Second, the separation of polysomes into free, cytoskeletal-bound and membrane bound classes may not result in completely pure fractions. Third, CG was not equipped with the information coding for a signal peptide and could not therefore be secreted. SSGG (Figure 3) and SSGA (Figure 6) are examples of truly targeted mRNA. Thus, contrary to the comments raised in the Office Action Figure 3 does provide additional support enablement of the invention.

Based on all of the above, the rejection of the claims under 35 USC §112, first paragraph is overcome and should be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 9-16 and 21 under 35 U.S.C. § 103(a) as being unpatentable over Hesketh *et al.(Biochem. J. 298*:143-148 (1994) ("Hesketh) in view of Sleep *et al.*, *Biotechnology* 8:42-46 (1990) ("Sleep") and further in view of Applicants alleged admission on the record (page 6 of the Response dated August 8, 2002). Applicants respectfully traverse the rejection.

Hesketh discusses the influence of the 3' untranslated region on mRNA localization by measuring the distribution of myc, β-globin and hybrid myc-globin mRNAs between free,

cytoskeletal-bound and membrane-bound polysome in cell transected with either control or chimeric constructs. In effect, Hesketh does no more than discuss the retargeting of mRNA (globin/c-myc) between free and cytoskeletal bound polysomes. The Examiner acknowledges that "Hesketh et al. do not teach the use of a signal sequence (e.g. albumin) to increase protein production." While Hesketh may discuss localization of various mRNA, he does ***not*** teach or suggest ***actively retargeting to the membrane-bound polysomes or constructing a nucleic acid molecule such as that in claim 9 that is capable of producing retargeting of RNA***.

The Examiner has also stated at page 4 of the Office Action that "Hesketh et al. teach that it is already well-known . . . that directional information for mRNAs is . . . present in their 3' UTR." In an attempt to support this position the Office Action pointed to Figure 2 of Hesketh. Regardless of the interpretation of the Figure presented in the Office Action, this still does not establish that Hesketh or anyone else knew about directional information being present in the 3' UTR. Applicants respectfully submit that as of the time that Hesketh was published, it was ***not*** well-known that in ***mammalian*** cells directional information for mRNAs was incorporated in the 3' UTR. If this rejection is maintained, Applicants respectfully request the Examiner to either specifically cite the place in Hesketh where such is taught or provide an appropriate cite to another reference to establish this alleged "well-known" fact.

While Hesketh may discuss that the 3' UTR takes part in mRNA targeting between free and cytoskeletal bound polysomes, there is nothing in the publication that teaches or suggests that competition could occur between nucleotide sequences coding for the signal

sequence and those of the 3' UTR. Therefore, there is no motivation or suggestion for one of skill in the art to combine Hesketh with Sleep.

Sleep describes the secretion of human serum albumin into the culture supernatant from yeast. Sleep also discusses that the choice of leader sequence and its relationship to the structural protein under study are of consequence to the success of this process. Sleep does ***not*** remedy the deficits found in Hesketh because it fails to teach or suggest ***disrupting or replacing*** the native 3'-UTR of a non-secreting protein. Therefore, combining Hesketh with Sleep still fails to render the claimed invention obvious.

The Examiner refers to Applicants' statement in the reply filed August 8, 2002 , "that it is 'well known' that 'in order to obtain secretion of an intracellular protein. . . a nucleic acid encoding a signal peptide [must] be attached to the mRNA encoding the intracellular protein." This statement, however, does nothing to remedy the deficits in either Hesketh or Sleep or provide a suggest to combine the cited art. The statement, still fails to render obvious claim 9 or a vector comprising the nucleic acid of claim 9:

> A nucleic acid molecule encoding a mammalian signal peptide operatively linked to a nucleic acid encoding a protein that would normally not be secreted from a mammalian cell, said signal peptide allowing at least some of said protein to be synthesized on the endoplasmic reticulum in a manner so that said protein can be secreted, the nucleic acid molecule comprising a deletion, insertion, or substitution in respect of all or part of a 3' untranslated region, relative to the corresponding region present in naturally occurring RNA encoding said protein, such that the region's effect in directing molecules to an intracellular location other than the endoplasmic reticulum or to free and/or cytoskeletal bound polysomes is eliminated or reduced relative to the corresponding naturally occurring sequence.

There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the art of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534 (Fed. Cir. 1998). "A general incentive does not make a particular result obvious, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USQP2d 1210, 1216 (Fed. Cir. 1995). The Examiner has failed to show any teaching or suggestion for combining the cited art.

The Examiner argues that "Sleep et al. do teach the use of a human serum albumin signal sequence to secrete a protein." (Office Action at page 5, first full paragraph). While this may be true, the HSA protein taught in Sleep *et al.* is a protein that is, in fact, normally secreted. This is in contrast to the claims which require that the protein "normally not be secreted from a mammalian cell." In addition, Sleep *et al.* relates to secretion in yeast cells rather than mammalian cells.

There is nothing in Sleep which teaches or suggests that the 3' UTR might override the effects of a signal sequence and result in inadequate retargeting of mRNA to membrane-bound polysomes. Further, Sleep does not even raise the issue of the effectiveness of targeting mRNA to membrane-bound polysomes nor do they take into consideration the possibility of signal sequence/3' UTR interaction, potentially affecting retargeting.

There is no suggestion in Sleep to use a different signal sequence other than the one described in the respective reference. Sleep *et al.* studied the effect of five specific signal sequences on the secretion of human serum albumin (HSA), a protein that is normally secreted. Sleep *et al.* state at page 45, column 1, second full paragraph, that "[t]he high

efficiency of all these leader systems in directing the secretion of HSA is likely to reflect the nature of HSA as a protein in that it is a ***naturally secreted product***. . . ." (Emphasis added). Given the positive results, there is no suggestion or teaching in Sleep *et al.* to use other signal sequences. Moreover, there is no suggestion in either reference to use a different protein other than the one being studied in each respective reference. The focus of Sleep is secreting HSA in yeast cells.

Regarding the expectation of success in combining the two references, the Examiner has stated that:

> [o]ne of ordinary skill in the art would have had a reasonable expectation of success in adding a nucleic acid sequence encoding a human serum albumin signal sequence as taught by Sleep et al. to the gene of Hesketh et al. since molecular cloning techniques were well-known and highly successful at the time of the present invention, as evidenced by their successful use by Sleep et al. And Hesketh et al.

(Paper No. 18, page 3.) Applicants respectfully disagree.

Merely because molecular cloning techniques were well-known, this does not provide a reasonable expectation of obtaining the claimed invention upon the combination of Hesketh and Sleep. Applicants have already described deficits in Sleep and Hesketh. Because of those deficits the combining of Hesketh and Sleep would not result in obtaining the nucleic acid as claimed in claim 9 or any of the subject matter claimed in the additionally rejected claims. Even if cloning techniques were well know, this still adds nothing to the combination of art that would result in a reasonable expectation of success.

Finally, Applicants again emphasize that the crux of the invention is the unexpected finding that efficient secretion of mammalian proteins can be obtained by making a deletion, insertion or substitution in the 3'-UTR of the native nucleic acid encoding the mammalian

protein. There is absolutely no teaching in either Hesketh or Sleep which suggests considering the effects that altering the 3'-UTR might have on the efficiency of secretion. Thus, the combination of references do not teach or suggest every element of the claims.

In view of the above, Applicants assert that the cited references do not render the claims obvious and therefore respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (202) 772-8589.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Lawrence B. Bugaisky

Lawrence B. Bugaisky
Attorney for Applicants
Registration No. 35,086

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1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600